REMARKS

Claims 1, 23, 45, and 50-52 have been amended, and claims 2-22, 24-40, 43, 44, and 49 have been cancelled without prejudice or disclaimer. Claims 1, 23, 41, 42, 45-48, and 50-53 are pending in the instant application. No new matter has been added as a result of the above-described amendments. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Objection to the Specification

The Office Action contains an objection to the specification for reciting "Figures 6A-6B" at page 6, line 38 rather than "Figures 6A-6E" to match the figure.

Applicants have amended the specification to recite "Figures 6A-6E" to match the figure. Applicants, therefore, respectfully request that this objection be withdrawn.

2. Substitution of New Title

The Office Action states that a new title is required that is clearly indicative of the invention to which the claims are directed.

Applicants have amended the title as suggested by the Examiner to read: "TNF Binding Proteins." Applicants, therefore, respectfully request that this objection be withdrawn.

3. Information Disclosure Statement

The Office Action states that certain references listed on the Information Disclosure Statement filed July 27, 2001 were not present, and therefore, have not been considered.

Applicants hereby file a Supplemental Information Disclosure Statement listing those references from the Information Disclosure Statement filed July 27, 2001 that have not yet been considered.

4. Rejection of claims 1-53 for double patenting

The Office Action provisionally rejects claims 1-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-76 of co-pending

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Application No. 09/792,356 (the '356 application). The Action states that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application has claims directed to TNF binding proteins and the '356 application has claims directed towards pharmaceutical compositions comprising the same TNF binding proteins, and therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to make pharmaceutical compositions comprising the TNF binding proteins in order to administer the polypeptides to individuals in order to ameliorate the effects of TNF.

Applicants respectfully disagree with the Action's assertion that since the instant application has claims directed to TNF binding proteins and the '356 application has claims directed towards pharmaceutical compositions comprising the same TNF binding proteins, it would have been *prima facie* obvious to one of ordinary skill in the art to make pharmaceutical compositions comprising the TNF binding proteins in order to administer the polypeptides to individuals in order to ameliorate the effects of TNF. However, because the instant Action has asserted only a provisional rejection of claims 1-53 under the doctrine of obviousness-type double patenting, Applicants elect to address this ground of rejection by submitting a Terminal Disclaimer or by argument upon notification that this rejection has been made non-provisional, all other conditions for patentability have been met, and the instant claims are otherwise in condition for allowance.

The Office Action also rejects claims 1-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33 and 34 of U.S. Patent No. 6,271,346 (the '346 Patent). The Action states that although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are directed to TNF binding proteins and the '346 Patent has claims directed towards pharmaceutical compositions comprising the same TNF binding proteins, and therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to make pharmaceutical compositions comprising the TNF binding proteins in order to administer the polypeptides to individuals in order to ameliorate the effects of TNF.

Applicants respectfully disagree with the Action's assertion that since the claims of the instant application are directed to TNF binding proteins and the '346 Patent has claims directed towards pharmaceutical compositions comprising the same TNF binding proteins, it would have been *prima facie* obvious to one of ordinary skill in the art to make pharmaceutical compositions

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comprising the TNF binding proteins in order to administer the polypeptides to individuals in order to ameliorate the effects of TNF. However, Applicants acknowledge the rejection of claims 1-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33 and 34 of the '346 Patent, and hereby elect to address this ground of rejection by submitting a Terminal Disclaimer or by argument upon notification that all other conditions for patentability have been met and the claims are otherwise in condition for allowance.

The Office Action also rejects claims 1-53 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-32 of the '346 Patent.

Applicants have amended claims 1-53 so that they are no longer coextensive in scope. Applicants, therefore, respectfully request that this rejection be withdrawn.

5. Rejections of claims 15-22 and 45-53 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 15-22 and 45-53 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

The Action first asserts that claims 15-22, 45-48, and 50-53 are indefinite because the "at least" language of the independent claim does not place an upper limit on the extent of the changes to be made.

Applicants respectfully disagree with the assertion that the term "at least" renders claims 15-22, 45-48, and 50-53 indefinite. However, in an effort to expedite prosecution of the instant application, Applicants have cancelled claims 15-22, rendering this ground of rejection moot with respect to these claims. With respect to claims 45, 46, and 48, Applicants contend that the term "at least" does not render these claims indefinite because claims 45, 46, and 48 are directed to recombinant polypeptides having the ability to bind TNF, wherein said polypeptides comprise an amino acid sequence as set forth in SEQ ID NO: 4, and wherein the recombinant polypeptides have additional amino acids at the amino-terminus, at the carboxyl-terminus, or at both the amino-terminus and carboxyl-terminus. Claims 45, 46, and 48, therefore, no longer encompass recombinant TNF binding proteins in which modifications have been made to the amino acid sequence of SEQ ID NO: 4. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claim 49 is indefinite because it encompasses a protein encoded

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by a nucleic acid molecule that hybridizes under "moderately or highly stringent" conditions, and there are no hybridization conditions defined in the specification.

Applicants respectfully disagree with the assertion that the specification does not define any hybridization conditions. In fact, the specification discloses that cDNA clones containing TNF binding protein coding sequences were isolated from a fibrosarcoma cDNA library by hybridization using a 0.4 kb probe isolated from the TNF-α induced fibrosarcoma cDNA library in 6x SSC, 5X Denhardt's, and 0.1% SDS for 16 hours at 65°C. However, in an effort to expedite prosecution of the instant application, Applicants have cancelled claim 49, rendering this ground of rejection moot.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment, and request that the Examiner withdraw all rejections made on this basis.

6. Rejection of claims 15-22, 45-48, and 50-53 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 15-22, 45-48, and 50-53 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The Action states that the specification, while being enabling for making and using a polypeptide comprising the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, does not reasonably provide enablement for making and using recombinant polypeptide variants of these sequences having at least one conservative amino acid substitution, at least one amino acid substitution at a glycosylation site, at least one amino acid substitution at a proteolytic cleavage site, at least one amino acid substitution at a cysteine residue, at least one amino acid deletion, at least one amino acid insertion, or a combination of these modifications. The Action also states that in the absence of information concerning those residues in the amino acid sequence of SEQ ID NO: 4 that are essential for its biological activity and structural integrity, a person skilled in the art would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional, and substitutional mutation analysis before that person could begin to rationally design a functional TNF binding protein variant.

The Action also asserts a rejection of claims 15-22, 45-48, and 50-53 under 35 U.S.C. § 112,

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first paragraph, in so far as the claims encompass an isolated protein other than a recombinant polypeptide comprising the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that because the specification merely discloses one polypeptide sequence, the written description does not support the claimed scope and does not fulfill the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicants respectfully disagree with the assertion that the specification does not enable a skilled artisan to use the invention commensurate in scope with the claims, or that that the specification fails to reasonably convey to a skilled artisan that the inventors had possession of the claimed invention at the time the application was filed. Applicants note that the specification sets forth the amino acid sequences of a TNF receptor polypeptide (page 5, lines 7-39) and a 161 amino acid portion of this sequence having the ability to bind TNF (page 5, line 45 to page 6, line 3). The specification also discloses that the first 29 amino acid residues of the TNF receptor polypeptide constitute the signal peptide (page 21, line 35 to page 22, line 2), and that amino acid residues 30-40 and 202-211 are proteolytically cleaved from the TNF receptor to form the TNF binding protein (page 22, lines 11-12 and page 23, lines 27-29). The specification teaches that techniques for making conservative substitutions are well known in the art (page 14, lines 13-15), and provides a list of exemplary conservative substitutions (page 15, Table 1). Applicants contend that they are under no duty under the statute to enumerate all of the species disclosed generically in their specification, particularly where, as here, the structure of the native molecule is disclosed, the types of variants of said structure are generically disclosed, and a functional property of the claimed molecule (TNF binding activity) and assays to assess species for said property are disclosed. The specification also teaches the location of glycosylation sites (page 22, lines 16-19), proteolytic cleavage sites (page 22, lines 26-28 and page 23, lines 27-29), and cysteine residues (SEQ ID NO: 2), wherein amino acid substitutions can be made.

Applicants also respectfully disagree with the Action's assertion that the claims of the instant application are analogous to claim 7 of U.S. Patent No. 4,703,008 (the '008 patent), which was held

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invalid for lack of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). In that case, the Federal Circuit noted that for inventions directed to DNA sequences, to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, the specification must disclose how to make and use enough sequences to justify the grant of the claims sought. *Amgen Inc.*, 927 F.2d at 1213. The Court determined that the specification of the '008 patent was insufficient to enable one of ordinary skill in the art to make and use the claimed invention because it disclosed how to make and use only a few of the nearly infinite number of erythropoietin variants encompassed by claim 7 (the trial court had found that a skilled artisan, by making substitutions at only three positions in the erythropoietin sequence, could generate over a million different erythropoietin variants). *Id.* Because the disclosure was limited to only a few erythropoietin variants, the specification failed to disclose how to make and use enough sequences to justify a claim encompassing *any* DNA sequence that encodes a polypeptide having erythropoietin-like activity. *Amgen Inc.*, 927 F.2d at 1213-14. In contrast, the instant application discloses, for example, a 161 amino acid portion of the TNF receptor polypeptide that possesses the ability to bind TNF; the locations of glycosylation sites, proteolytic cleavage sites, and cysteine residues; and a list of exemplary conservative substitutions. Applicants respectfully contend that because the specification discloses how to make and use enough sequences and enables one skilled in the art to carry out the invention commensurate with the scope of the claims, the claims of the instant application are not analogous to claim 7 of the '008 patent.

Applicants also note that the independent claims as-filed contained an explicit limitation to encompass only those molecules that possess a particular activity, namely, the *ability to bind TNF*. The specification defines the "ability to bind TNF" as "the ability of a protein to bind to TNF-α in such a way that TNF-α is prevented from binding to the functional part of the receptor and the activity of TNF-α in humans or animals is inhibited or prevented altogether" (page 17, lines 23-28). In view of the explicit limitation that the claimed molecules possess the ability to bind TNF, Applicants also respectfully disagree with the Action's assertion regarding the specie of substituted molecule having conservative substitutions at every amino acid position. The Action asserts that by making conservative amino acid substitutions at every residue, one of ordinary skill in the art can prepare a polypeptide comprising an amino acid sequence that completely differs from the

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polypeptides disclosed in the instant specification and expect it to have the same functions as the polypeptides disclosed in the instant specification. Applicants contend that one of ordinary skill in the art would appreciate that a polypeptide prepared by making conservative amino acid substitutions at every residue would not have the same functions as the unsubstituted polypeptide. Applicants contend that in view of the instant specification's teachings (as discussed above), one of ordinary skill in the art would readily be able to determine which TNF binding protein variants have the ability to bind TNF, and therefore, that it would not require undue experimentation for one of ordinary skill in the art to determine which TNF binding protein variants fall within the scope of the instant claims.

While Applicants respectfully disagree with the Action's assertion that the specification does not reasonably provide enablement for making and using recombinant polypeptide variants of the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20, and further, with the Action's assertion that the specification does not convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention, Applicants have amended claims 1, 23, 45, and 50-52 and have cancelled claims 2-22, 24-40, 43, 44, and 49 in an effort to expedite prosecution of the instant application. Applicants, therefore, respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

7. Claim of priority

The Office Action asserts that the amino acid sequences set forth in SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, and SEQ ID NO: 20 are entitled under 35 U.S.C. § 119(a) to the benefit of the June 21, 1989 filing date of German Patent Application No. P39 20 282.8. The Action also asserts that the amino acid sequence set forth in SEQ ID NO: 2 is entitled under 35 U.S.C. § 119(a) to the benefit of the April 6, 1990 filing date of European Patent Application No. 90106624.1.

Although Applicants respectfully disagree with each of the Action's priority determinations, Applicants contend that neither determination is relevant to the rejections made in the instant Action. Applicants, therefore, acknowledge the Action's priority determinations, and elect to address these

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determinations when either determination becomes relevant to the patentability of the instant claims.

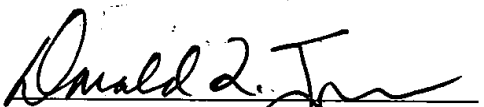
CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner O'Hara believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: March 17, 2004

By: 
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